PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 37/02, 37/12, 47/26

A1

(11) International Publication Number: WO 92/13547

(43) International Publication Date: 20 August 1992 (20.08.92)

(21) International Application Number: PCT/US92/00723

(22) International Filing Date: 28 January 1992 (28.01.92)

(30) Priority data:
652,091 7 February 1991 (07.02.91) US

(71)(72) Applicants and Inventors: EATON, Alexander, Mellon [US/US]; 910 Constitution Drive, Apt. #220, Durham, NC 27705 (US). BASS, Lawrence, Samuel [US/US]; 42-15 Westmoreland Street, Little Neck, NY 11363 (US). LIBUTTI, Steven, Kenneth [US/US]; 4 Horizon Road, Apt. #602, Fort Lee, NJ 07024 (US).

(74) Agent: KIPNES, Allen, R.; Watov & Kipnes, P.O. Box 247, Princeton Junction, NJ 08550 (US).

(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent).

Published
With international search report.

(54) Title: DRUG DELIVERY COMPOSITION AND METHOD OF USING THE SAME

(57) Abstract

A drug delivery composition and method of administering in which the composition contains at least one peptide and at least one second component which is adapted to support the peptide upon the application of energy to the composition, wherein the rate at which the drug is released from the composition may be controlled and/or the drug may be delivered to a particular or targeted area of the body.

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DRUG DELIVERY COMPOSITION AND METHOD OF USING THE SAME

FIELD OF THE INVENTION

The present invention is directed to a vehicle for delivering an active component such as a drug to a particular site in the body, particularly at a substantially continuous rate. The present invention is also directed to a vehicle for systemic delivery of the active component in a continuous release or controlled release manner. The present invention is also directed to a process for production of the composition into a number of different forms. Compositions employing the drug delivery vehicle and methods of administering the same are also part of the present invention.

BACKGROUND OF THE INVENTION

In recent years interest has increased in systems for the delivery of drugs which reduce drug toxicity and increase drug efficacy. Systems have been developed which enable drugs to be delivered to specific targets or body sites. This improves efficacy of drug delivery and decreases systemic toxicity. Some drug delivery systems have been developed to control the rate at which the drug is delivered which is particularly desirable for highly toxic drugs, and drugs with a short half-life which require frequent administration. Highly toxic drugs can also be delivered at therapeutic or high local levels, without the development of toxic body levels.

Existing systems for targeted drug delivery include polyanionic polymers for attachment to mucin, and fibrin glue for attachment to soft body tissues. (See J.R. Robinson et al. "Bioadhesive Polymers for Controlled Drug Delivery", Ann. NY Acad. Sci. 507:307-314,1987). Polyanionic polymers, such as polyacrylates, are attached to mucin to form a drug delivery system. The attachment of a material to the mucin coating of a cell is known as mucoadhesion. A number of compounds have been used for their mucoadhesive properties including

carboxymethylcellulose, carbopol, polycarbophil, sodium alginate, gelatin, pectin, acacia, and povidone.

The ability of mucoadhesives to adhere to mucin varies. For example, carboxymethylcellulose, carbopol, polycarbophil and sodium alginate are excellent adhesives while pectin, acacia and povidone are poor adhesives. Even if a mucoadhesive has excellent adhesive properties, its use is limited to delivery sites where mucin is present, such as the intestine and mouth.

Fibrin glue is another vehicle that may be used as a targeted drug delivery system. (See Deyerling et al. "A Suspension of Fibrin Glue and Antibiotic for Local Treatment of Mycotic Aneurysm in Endocarditis - an Experimental Study." Thor. Cardiovasc. Surg. 32:369-372, 1984) discloses the use of a fibrin glue antibiotic mixture for the targeted delivery of antibiotics to treat mycotic aneurysms in endocarditis.

Fibrin glue, however, has limited application to drug delivery because it must be obtained from pooled blood samples. Products obtained from pooled blood samples expose the recipient to the risk of infection from AIDS, Hepatitis A, B and C, Cytomegalovirus, Jakob-Crueutzfeld disease, and other diseases. In the United States, the threat of infection has outweighed the benefits of obtaining commercial quantities of fibrin adhesives. As a result, the production of fibrin has been limited to quantities obtained from a patient's own blood to reduce the risk of infection. In addition, fibrin glue has poor handling characteristics and non-uniform yield and activity. These limitations make the use of autologous fibrin adhesives costly, time consuming, and unreliable, and therefore, of limited value.

Like targeted drug delivery systems, controlled drug delivery systems are designed to optimize the delivery of therapeutic materials to the body in order to maintain uniform blood drug levels or tissue levels over time and to reduce the frequency of administration. R.S. Langer et al., Biomaterials 2:201-214, 1981 lists the advantages of controlled drug delivery

which include: 1) maintenance of plasma drug levels in therapeutically desirable ranges; 2) reduction of harmful systemic side effects; 3) protection of drugs with a short half-life from degradation; 4) reduction of patient discomfort compared to conventional dosage administrations; 5) reduction in the amount of drug used; and 6) improved patient compliance.

Control drug delivery systems are generally classified according to the means by which delivery of the drug is rate limited. For example, diffusion-controlled systems are those typically employing reservoirs in which the drug is encased within a polymer film. Delivery of the drug is controlled by the rate at which the drug passes through the film. Polymers particularly suitable for diffusion controlled systems include silicon rubber, hydrogels such as Hydron™, and ethylene-vinyl acetate copolymers e.g. Ocusert pilo -20 and 40 manufactured by Alza Corporation.

Diffusion-controlled systems are disadvantageous because the polymers most suitable in such systems are not readily biodegradable and therefore must be surgically implanted and removed. Use of these polymers raises concern of long term toxicity and cosmesis if the implant is superficial. In addition, high molecular weight drugs such as insulin have difficulty passing through the film at a controlled rate and therefore can not readily be delivered in this manner.

Another type of system is chemically-controlled delivery, which includes bioerodable systems and pendant chain systems. In bioerodable systems, the drug is encased within a polymer, which degrades over time allowing the drug to escape. Such systems are disadvantageous because the absorption products may be toxic, immunogenic or carcinogenic. Examples of degradable polymers used in bioerodable systems include water insoluble polymers having degradable crosslinks, or which may be stabilized by, for example, hydrolysis, ionization, or protonation of the pendant side groups or which may be solubilized by backbone chain cleavage to smaller water soluble

molecules. Specific examples of such polymers include polylactic acid, lactic/glycolic acid copolymers, polyvinylpyrrolidine, polyorthoesters, poly (e-caprolactone) and polyaminoacids.

In pendant chain systems, a drug is chemically bound to a polymer backbone-chain and released by hydrolytic or enzymatic cleavage. These systems offer the advantage that over 80% of the system by weight can be the drug itself. An example of a pendant chain system are polyaminoacids containing steroids as pendant side chains.

In another system, known as a swelling-controlled system, a drug is dissolved in a polymer solution and then the solvent is evaporated leaving the drug dispersed in a glassy (solvent-free) polymer matrix. As the dissolution medium (e.g. water) penetrates the matrix, the polymer swells and its glass transition temperature is lowered. As a consequence, the swollen polymer allows the drug to diffuse outwardly. An example of a polymer useful in such a system is polyvinylalcohol.

Magnetic particles have also been used in drug delivery systems in which the particles are uniformly dispersed within a polymer matrix such as an ethylene-vinyl acetate copolymer.

Collagen has been used as a vehicle for drug delivery systems. For example, Hardy, Reissue Patent No. 26,963 discloses an injectable drug vehicle made of a reconstructed collagen fluid adjuvant. The adjuvant increases in viscosity upon entry into the recipient and thereafter substantially completely dissociates in the body at a relatively slow rate.

Teruo Miyata et al., U.S. Patent No. 4,164,559 discloses a drug delivery device employing a chemically modified collagen membrane which is soluble under the conditions of administration and is particularly suited for ophthalmic applications.

Helmut Wahlig et al., U.S. Patent No. 4,291,013 discloses a mixture of collagen which can be worked into a desired shape under pressure and/or heat. The resulting material can be shaped into tubes, strands, foils or tablets of various

sizes. This vehicle releases the drug at protracted rates continuously without the damaging side-effects normally associated with implants. The binding agents which may be used in this vehicle include polymers and copolymers of glycolic acid and lactic acid.

Despite the quantity and diversity of drug delivery systems, their use has been limited. The polymers used as the matrix material are often toxic and/or lack bicompatibility. In addition, some systems produce harmful byproducts or lack sufficient control over the release of the drug. In addition, the physical state of the composition can not be altered making it difficult to administer the composition.

It is therefore an object of the present invention to provide a drug delivery vehicle which may be used for the targeted delivery of the drug to specific tissues.

It is another object of the invention to provide a drug delivery vehicle which may be used for the controlled release of a drug locally to targeted tissues or systematically to the entire body.

It is a further object of the invention to provide a drug delivery vehicle that is non-toxic and/or biocompatible.

It is another object of the invention to provide a drug delivery vehicle which can be activated by the addition of energy to change the drug release and/or physical characteristics of the vehicle.

It is a further object of the invention to provide a drug delivery vehicle which can be activated by the addition of energy to localize the attachment of the vehicle to specific tissues.

It is another object of this invention to provide a production process for such a drug delivery vehicle.

SUMMARY OF THE INVENTION

The present invention is directed to a composition suitable for releasing a drug contained within the composition over a period of time systemically to the entire body and/or for delivering the drug locally to specific target tissues. The drug-containing composition can be administered internally or topically depending on the drug and the purpose of administration. The invention also provides a production process for the composition, and its formulation into a number of different forms.

The composition may be formulated as a solid such as in the form of tablets, pellets, powder, optical lenses, sheets, pads, patches and the like. The composition may also be made in the form of a liquid or quasi-liquid, such as a solution, paste, gel and the like. The composition may also be made in the form of a sponge or porous material. The composition may be administered or applied alone or may be incorporated in another known chemical or mechanical delivery system. This includes, but is not limited to, encapsulation, surrounded by a diffusion membrane, imbued into implantable prostheses (i.e. vascular grafts, prosthetic joints, mesh fabric for hernia repairs), imbued into bandages (i.e. gauze bandages, plastic or biomembrane bandages) or applied as a liquid or gel held in place by overlying occlusive or breathable (porous) device such as a bandage or drug delivery patch. The composition may also be instilled or applied alone, and then fixed into place by the administration of energy, as for example, heat, laser light, or electrical energy (i.e. electrocautery).

The composition comprises at least one first primary component which has a physical conformation which can be altered by the application of energy, such as heat to retain the drug in the vehicle and optionally facilitate a delayed release of the drug. More specifically, the first primary component is selected from natural or synthetic peptides, hydrolyzed or oxidized

derivatives thereof, or chemically or enzymatically modified, cleaved or shortened variants thereof, cross-linked derivatives thereof and mixtures thereof. Included among the peptides are structural proteins, serum proteins and mixtures thereof. Examples of the proteins are collagen, albumin, α-globulins, ß-globulins, -globulins, transthyretin, elastin and fibronectin and coagulation factors including fibrinogen, fibrin and thrombin.

The second primary component is generally selected from at least one compound which supports the first component. Upon the application of energy such as heat, the conformation of the first and second components is altered producing a new interrelationship or interaction between the respective molecules. This interrelationship modulates the physical properties of the composition including: (1) the binding and release properties of the drug incorporated in the composition; (2) the handling characteristics of the composition; (3) the binding of the material to tissues for targeted drug delivery; and (4) combinations thereof. The second component is preferably selected from proteoglycans, glycoproteins, protein gels, gelatins, saccharides, and polyalcohols. Natural or synthetic derivatives, enzymatically or chemically modified, cleaved or shortened variants, salts, cross-linked, oxidized or hydrolyzed derivatives, or subunits thereof may also be used.

Proteoglycans are preferably natural or synthetic non-cellular body matrix materials found in the interstices between cells such as hyaluronic acid, salts of hyaluronic acid including sodium hyaluronate, chondroitin sulfate, dermatin sulfate, keratin sulfate, heparin and heparin sulfate. The protein gels and gelatins include collagen and elastin, respectively. Other proteins which may exist in a gel-like state include caseinates, and blood derived substances such as fibrin and fibrinogen. The saccharides are preferably selected from oligosaccharides such as fructose and polysaccharides such as hydroxypropylmethylcellulose, carboxymethylcellulose, dextrans,

agarose, alginic acid, and pectins. The preferred polyalchols are glycerine, mannitol and sorbitol.

The composition contains at least one drug or other desirable active ingredient which is to be delivered to the recipient under controlled release conditions and/or to a targeted area.

In accordance with the invention, the composition is either provided with energy such as heat prior to delivery or after its placement into a warm blooded animal to a temperature sufficient to alter the physical characteristics of the composition in a manner which changes the rate at which the drug is released from the composition, and/or alters the mode of administration, and/or binds it locally to a substrate such as tissue or prosthesis for targeted delivery. In the case where the composition is preheated prior to administration, the viscosity of the material may be controlled so as to provide a range of physical states for the composition which can be selected according to the particular application. The composition of the present invention can be formulated to produce the handling characteristics desired both before and after energy application by: (1) Varying the concentration and/or components of the composition of the present invention; (2) Varying the number of cross-links between molecules or within molecules of the components of the composition; (3) Varying the molecular weight of the subunits of the composition; (4) Varying the water content of the composition. As mentioned above, the process of inputting energy such as heat itself alters the physical handling characteristics to produce a variety of physical states for different clinical applications. The peak energy level, rate of energy input (power), rate of reduction in energy input and the duration of energy input, the presence or absence of gas bubbles and the pressure at which energy is input, may be varied to effect the final state of the composition produced. When heat is used, the variables include maximum temperature, rate of heating, duration of heating,. gas bubble content, and the

pressure under which heating is performed.

Types of energy which may be delivered to the composition of the present invention to impart the desired changes in the physical characteristics of the composition, include but are not limited to, electrical energy such as electrocautery, heat guns, heated probes, heated fluids, sound energy such as ultrasound, and other electromagnetic radiation such as microwaves, monochromatic coherent light, monochromatic non-coherent light, polychromatic coherent light, polychromatic non-coherent light, in a continuous or non-continuous fashion.

DETAILED DESCRIPTION OF THE INVENTION

The composition of the present invention can be prepared in a variety of forms for delivering an active component such as a drug to a particular location. In addition, the drug may be released from the composition over time to maintain more uniform blood or tissue levels of the drug, and to reduce the need for frequent dosing. Controlled release of the drug may be obtained for both systemic drug delivery, and for targeted drug delivery to focal areas of tissue, depending on the formulation of the material and the method of administration.

As used herein the term "drug" is used in its broadest sense and generally refers to any prophylactic or therapeutic medication that can be administered to a warm blooded animal for some useful purpose. By way of example, the term "drug" includes antibiotics such as gentamicin, vasoactive substances such as epinephrine, anticoagulants such as coumadin, anti-inflammatory agents such as steroids, hormones such as growth factors, insulin, and angiogenesis factors, chemotherapeutic agents such as methotrexate and 5-fluorouracil, and enzymes such as streptokinase and the like. One or more drugs may be present in the composition of the present invention.

The composition may be injected or implanted subcutaneously or intramuscularly for creation of a depot for

systemic administration of a medication in a controlled manner. Targeted or topical administration of the composition is also possible, including topical application to open skin wounds, instillation into abscesses, subconjunctival or intravitreal injection, internal application on or around vascular and intestinal anastomoses, nerve repairs, and suture sites and the like.

The composition may be incorporated within another known delivery system. These include, but are not limited to, encapsulation, diffusion through a porous or nonporous membrane, bioerodable system, and swelling delivery systems, as well as transdermal patches and the like. The composition may be applied topically and sealed in place with an overlying bandage, occlusive, or porous/breathable membrane.

The composition may be externally bound to implants such as prosthetic joints. It may be bound to or secured within the interstices of porous implants such as vascular grafts, prosthetic mesh fabric/sheets (e.g. as used for hernia repair). As a result, the drug is administered locally or systemically to treat the patient. For example, when an antibiotic is used in the composition, it may be secured to a prosthetic material through the application of heat in order to prevent infection. In addition, the composition may be bound to or imbued in gauze or other bandage dressings.

External application of the composition can be made directly as a liquid, solution, paste, gel patch, membrane, powder, plug, or pad and the like. The composition may be incorporated into a bandage, transdermal patch, or covered by occlusive membrane to a wound site to deliver growth factors to speed healing, angiogenesis factors to improve blood supply to poorly vascularized wounds, steroids to minimize scar formation, antibiotics to prevent or cure infection and the like. The application of drugs such as antibiotics, steroids, antimetabolites, and growth factors to the eye in the form of contact lenses, patches, injectables, or drops, may serve a

similar purpose as well as being non-allergenic, and biodegradable.

Vasodilators, vasoconstrictors, and growth factors are some of the drugs that can be delivered to vascular anastomoses. Prosthetic implants can be treated with anticoagulants and antibiotics using the present composition. In these examples, and in other applications, the composition of the present invention can be formulated in a particular physical state to facilitate delivery and/or controlled release of the drug.

The peptide component of the present invention is preferably selected from collagen, albumin, and mixtures thereof. Examples of collagen materials include, single stranded collagen, helical collagen, microfibrillar or fibrillar collagen, and gelatin (a hydrolysis product of collagen, cross-linked and non-cross-linked). Examples of albumin include human serum albumin and milk albumin. Examples of fibrinogen and fibrin, which can be used, but currently are not preferred due to the aforementioned problems include human, bovine and porcine fibrinogen and fibrin, respectively. However, should these problems be overcome by new production and/or purification techniques, fibrinogen and fibrin could be used in the present invention.

The amount of the peptide component is generally in the range of from about 0.1 to 95% by weight, preferably from about 1 to 35% by weight based on the total weight of the composition. One or more peptides may be present in the composition of the present invention.

The second component includes those compounds which possess properties to varying degrees which are important to targeted drug delivery and/or the controlled release of a drug. One or more second component materials may be present in the composition of the present invention. The preferred proteoglycans are hyaluronic acid and salts thereof, chondroitin sulfate, dermatin sulfate, keratin sulfate, heparin and heparin sulfate. The proteoglycans are generally present in an amount

of from about 0.01 to 75% by weight, preferably in the range of from about 0.1 to 40% by weight based on the total weight of the composition.

The preferred saccharides are those selected from polysaccharides such as carboxymethylcellulose, hydroxypropylmethylcellulose, dextrans, agarose, alginic acid, and pectins. The amount of the saccharides is generally in the range of from about 0.01 to 70% by weight, preferably in the range of from 0.1 to 40% by weight.

Preferred polyalcohols are those selected from glycerine, mannitol and sorbitol in a weight range of from about 0.1 to 90% by weight, preferably about 20 to 70% by weight.

Collagen as one of the preferred peptides is the most abundant protein in the body. When heated it can be denatured, and solubilized for easy application, such as by injection as a liquid solution. When cooled, collagen is partially renatured, resulting in a gel formulation. The temperatures at which gelling occurs can be controlled through the use of cross-linkage. Increasing the cross-linkage, increases the gelatin to liquid transition temperature, thereby, increasing the temperature needed to obtain, a liquid, injectable material. Decreasing the degree of crosslinking, has an opposite effect.

There are five types of collagen, each containing three polypeptides of about 1,000 residues per chain. The main function of collagen is to maintain the shape and to resist the deformation of the tissues. Through heating, collagen can be solubilized and easily injected or applied, and by cooling it can be turned into a gel which remains localized after injection, thereby providing drug delivery locally to the injection site. Collagen can also be rendered in a sterile form having a long shelf life. Collagen, therefore, is an ideal protein component of the present invention.

Albumin, another of the preferred peptides, is a transport protein with a molecular weight of 66,500 Daltons, and a half-life of 15-20 days. It accounts for 70-80% of the colloid

osmotic pressure of the plasma, and is distributed throughout the extracellular water. More than 60% of human albumin is located in the extravascular fluid compartments. When heated, albumin readily changes into a solid, making it an ideal substance for use in the present invention.

Because it is a transport protein, albumin binds naturally occurring therapeutic and toxic materials, as well as many pharmacologic agents. This property makes it ideal for drug delivery applications. A detailed discussion of the binding characteristics of human serum albumin can be found in Thomas E. Emerson, Jr., "Unique Features of Albumin: A Brief Review" Crit. Care Med. vol. 17 no. 7 pp, 690-694 (July, 1989), incorporated herein by reference.

Albumin when used in the present composition, provides distinct advantages over compositions using fibrinogen or other products obtained from pooled blood samples which may expose the recipient to the risk of infection. The use of albumin as a first component of the present invention, while obtained from pooled blood products, does not expose the patient to these risks. Human albumin, unlike human fibrin and fibrinogen, can be rendered free of infectious agents. Moreover, human albumin is more stable than its fibrin counterpart, both on the shelf and in vivo. This is because fibrinogen can be activated by thrombin and calcium, which are both present in the blood and other body tissues.

The preferred polysaccharides have a high molecular weight and form long chain molecules which produce viscous, gel-like materials at low concentrations. Low molecular weight, small chain polysaccharides require higher concentrations to produce viscous, gel-like materials, and tend to be less desirable. One of the preferred polysaccharides is hydroxypropylmethylcellulose which is preferably used in a sterile aqueous solution. As a sterile solution it may be formulated to have a molecular weight exceeding 80,000 daltons and a viscosity of at least about 4,000 centipoise. See, for

example, Thomas J. Liesegang et al., "The Use of Hydroxypropyl Methyl Cellulose in Extracapsular Cataract Extraction with Intraocular Lens Implantation", Am. J. Ophth. vol. 102 pp. 723-726 (December, 1986), incorporated herein by reference.

Another preferred polysaccharide is carboxymethylcellulose, which is also preferably used in a sterile aqueous solution. As a sterile solution it may be formulated in a 1% aqueous solution to have a viscosity of 10-3,000 centipoise or higher depending on its molecular weight. For example, a 2% aqueous solution of 45,000 daltons has a viscosity of 10-20 centipoise, a 2% solution of 100,000 daltons has a viscosity of 400-800 centipoise, and a 1% aqueous solution of 200,000 daltons has a viscosity of 1500-3000 centipoise.

Another preferred polysaccharide is dextran, which is also preferably used in a sterile aqueous solution. Generally, a sterile solution may be formulated using dextran having a molecular weight of 10,000 to 40,000,000 preferably 40,000 to 2,000,000 daltons. Dextran sulfate may also be used.

Another preferred polysaccharide is alginic acid, which is also preferably used in a sterile aqueous solution. As a sterile solution it may be formulated into a 2% solution having a viscosity of 250 to 14,000 centipoise or higher, depending on its molecular weight. For example, a 2% solution of alginic acid weighing 200,000 daltons has a viscosity of 14,000 centipoise, a 2% solution of (150,000 daltons) alginic acid has a viscosity of 3,500 and a 2% solution of alginic acid weighing 100,000 daltons has a viscosity of 250 centipoise. Pectin is another preferred saccharide, which can be formulated into an aqueous solution.

The preferred group of compounds under the general class of proteoglycans and derivatives thereof have a high molecular weight and form long chain molecules which produce viscous, gel-like materials at low concentrations. In particular, glycosaminoglycans which include hyaluronic acid and salts thereof, particularly sodium hyaluronate and chondroitin

sulfate, are preferred.

Hyaluronic acid is a polymer centered in the extracellular matrix of animals and humans. It is thought to form the filamentous backbone of both cartilage and other connective tissues and is a member of a group of materials known as ground substances.

Although ground substances are ideally suited as components in a drug delivery composition because of their physical properties, they have less than desirable drug binding characteristics (M.L. Mc Dermott, et al. "Drug Binding of Ophthalmic Viscoelastic Agents". Arch. Ophth. 107:261-263, 1989), incorporated herein by reference, unless they are combined with a peptide and heated, as described in the present invention.

Hyaluronic acid has a molecular weight of 4 to 80 x 10^6 daltons. Structurally hyaluronic acid is characterized by repeating disaccharide subunits of D-glucuronic acid with D-glucosamine, which are linked together to form layer polymers. Each subunit has one negative charge, which may help to explain its bond enhancing affect for targeted drug delivery. (See Principles of Biochemistry: Mammalian Biochemistry, 7th edition, edited by Emil Smith et al., pp. 7 and 229 (1983), incorporated herein by reference.

Hyaluronic acid and its salts have other advantages. In purified form, sodium hyaluronate has a viscosity of 40,000 centipoise at a sheer rate of 2 $sec.^{-1}$ at 25°C, and over 200,000 centipoise at a shear rate of zero. This non-Newtonian, or pseudoplastic viscous property of hyaluronic acid makes it ideal for forming a targeted drug delivery vehicle. At high shear rates, such as occurs during injection through a syringe, the viscosity of hyaluronic acid is low, facilitating injection. This allows for its easy application to tissues. At low shear rates, such as after application to tissues, its viscosity is high, which keeps it localized on the area to which it is applied. When applied as a component in a mixture with a peptide and a drug, the resulting composition can be readily bound to

tissues through an external energy source.

Chondroitin sulfate is a polymer centered in the extracellular matrix of animals and humans. It has a molecular weight of 5,000 to 50,000 daltons, and is composed of a repeating disaccharide subunit of D-glucuronic acid with D-galactosamine, which are linked together to form large polymers.

Chondroitin sulfate, like hyaluronic acid, is highly viscous in concentrations of 50 mg/ml, where its viscosity is 4000 cps (at shear rate of 2 sec^{-1}, 25°C).

The composition of the present invention can additionally contain viscosity modifiers in accordance with the end use of the composition. For example, the addition of viscosity modifiers provides a composition with a viscosity particularly suited to tissues which are to be repaired or sealed. Preferred viscosity modifiers include compounds previously mentioned which are non-cellular body matrix compounds such as hyaluronic acid and salts thereof of such as sodium hyaluronate, saccharides such as hydroxypropylmethylcellulose, fructose, carboxymethylcellulose, dextrans, agarose, alginic acid and pectin.

For control of the compositions handling characteristics, the use of long chain molecules, particularly saccharides, and proteoglycans, is advantageous. As the concentration of these molecules, or their molecular weight at a fixed concentration, is increased, higher viscosity and gel-like materials tend to be produced. (See E.L. Smith et al. "Connective Tissue, Collagen, Elastin, Proteoglycans, Fibronectin "Principles of Biochemistry, Mammalian Biochemistry (Chapter 6, 7th Edition. McGraw-Hill, pp 211-242, 1983 incorporated herein by reference). As the concentration of these molecules, or their molecular weight at a fixed concentration, is decreased, lower viscosity, more watery materials tend to be produced. Therefore, through modulation of the long chain molecule's molecular weight and/or concentration, the handling characteristics of the composition can be controlled to suit the desired application.

Compositions in which thick, viscous handling characteristics are desirable can be formulated by increasing the molecular weight and/or concentration of second component. Whereas those in which a thin, liquid, watery formulation is desirable can be formulated by decreasing the molecular weight and/or concentration of the second component. Applications in which a thick composition may be desirable include, but are not limited to, targeted drug delivery to abscesses, or for chemotherapy. Applications in which thin compositions may be desirable, include but are not limited to, the coating of porous grafts, or other implantable materials.

For targeted drug delivery, in which the composition is to be bonded to the tissues in situ, the use of certain second component materials is advantageous to enhance bonding. In particular, the use of mucoadhesives such as carboxymethylcellulose, sodium alginate, or other charged or neutral polymers facilitates bonding of the drug delivery composition to the tissues both before and after heat application. The use of these materials is most advantageous on mucin containing surfaces, such as the gastrointestinal tract, and the pulmonary system. Use of these materials on other surfaces, such as those with a high collagen content, which have a large concentration of hydroxyl groups, such as that imparted to collagen through 4-hydroxyproline, may also be advantageous in facilitating bond formation and targeted drug delivery. It is believed the mucoadhesive molecules tend to attach to mucin through the entanglement of the polymer chains with mucin on the surface of the tissue, and unionized carboxylic acid groups and hydroxyl groups on the polymer may form hydrogen bonds to the mucin or other molecules such as collagen. It is believed a high charge density is preferred for both swelling and hydrogen bonding for firm attachment to occur. (See Robinson JR, Longer MA, Veillard M. Bioadhesive polymers for Controlled Drug Delivery. Ann. NY Acad. Sci. 507:307-314, 1987, incorporated herein by reference.) Use of these materials as components of

the present invention, therefore should be advantageous to facilitate the bonding of the composition to the desired tissue surface, particularly before its activation with energy for targeted drug delivery.

The composition of the present invention may also include chromophores to facilitate visualization of the material during placement into warm blooded animals. Use of a chromophore will allow material which becomes displaced from the desired application site to be easily visualized, and subsequently removed using a cellulose sponge, gauze pad, or other absorbing material. Use of chromophores for aid in the placement of fibrin glue has been previously described, and may be employed in a similar manner to visualize the drug delivery compound (See I. Nasaduke I, et al. "The Use of Autogenous Rabbit Fibrin Sealant to Plug Retinal Holes in Experimental Detachments". Ann. Ophth. 18:324-327, 1986), incorporated herein by reference. Chromophores that may be used, include, but are not limited to fluorescein isothiocyanate, indocyanine green, silver compounds such as silver nitrate, rose bengal, nile blue and Evans blue, Q-Switch II™, a dye made by Kodak, Inc., Sudan III, Sudan black B and India Ink. The chromophores are preferably present in the composition in an amount of from about 0.01 to 50% by weight based on the total weight of the composition.

The present invention may also include substances which alter the absorption characteristics of the composition so that the composition absorbs energy at lower energy levels. This enables heating of the material using certain lasers whose energy would otherwise not be absorbed by the composition of the present invention, and allows the composition to be welded to the target tissues using these lasers. The bonding and sealing of tissues using a composition similar to that described herein is set forth in Applicants' copending application U.S. Serial No. 07/560,069 filed July 27, 1990, incorporated herein by reference. These substances reduce possible collateral damage to adjacent tissues typically associated with high energy level activators such as

laser beams. (See, "Mehmet C. Oz et al., "Tissue Soldering by Use of Indocyanine Green Dye-enhanced Fibrinogen with the near Infrared Diode Laser", J. Vasc. Surg. vol. 11 no. 5 pp. 718-725 (may, 1990); and B. Jean et al., "Target Dyes in Ophthalmology - Parts I and II", Lasers and light in Ophthalmology vol. 3 no. 1 39-52 (1990), incorporated herein by reference. Dyes such as indocyanine green, fluorescein and the like are particularly suited for this purpose. These dyes also may increase adhesivity, weld strength and viscosity. The dyes are preferably present in the composition in an amount of from about 0.01 to 50% by weight based on the total weight of the composition.

The addition of such dyes which have a peak light absorption at a specific wavelength, allows for the selective activation of the composition at the delivery site, while substantially reducing the risk of undesirable collateral thermal damage to adjacent tissues. By selecting a wavelength of light, emitted from a light source such as laser beam, which matches the peak absorption wavelength of the dye used, a lower threshold of input energy is needed to obtain the desired activation of the composition. By selecting a dye-energy wavelength combination in which the wavelength is not absorbed by the adjacent tissues, collateral injury to adjacent tissues can be further reduced. As an example, indocyanine green is a dye that selectively binds to human or animal albumin and has a maximum absorbance at 805 nm in an albumin solution. When the dye is mixed with albumin, continuous wave diode laser light, which is commercially available at 808 nm wavelength, can be selectively used to heat and coagulate the albumin. The peptide used as the first component of the present composition may be selected based on the selection of a particular laser-dye combination.

Other dye-laser combinations, include, but are not limited to, fluorescein isothiocyanate (Absorbance 490 nm) and an argon laser operating at 488-514 nm; silver compounds such as silver nitrate and a krypton laser (676 nm); dye compounds such as rose bengal, nile blue and Evans blue and Dye lasers absorbing

in the range of 200 to 610 nm. Q-switch II™ a dye manufactured by Kodak Inc., absorbs light from a Nd:YAG laser at 1064 nm and 1320 nm. Broad band absorbers, Sudan III, Sudan black B and India Ink and other black compounds may also be utilized to selectively adsorb light from any of the above-mentioned lasers.

The chromophores (dyes) in addition to providing an increase in weld strength, adhesivity, or viscosity may also increase the rate and ease of mixing and homogenizing the composition. The dyes may increase the degree of drug binding or otherwise modulate the release characteristics of the drug from the composition. This may in part result from the polyanionic structures of these compounds. Similarly, polyvalent cations, such as calcium, may act to increase the interrelation and/or binding of the first and second components to each other and the drug, particularly when the components are negatively charged. Use of polyvalent cations may facilitate the speed of mixing, homogenization of the material and may also modulate drug release.

Non-coherent light sources such as infrared, ultraviolet or polychromatic white light may also be used to deliver energy to the composition.

By heating the composition of the present invention the physical properties of the composition can be altered so that the desired handling characteristics, physical form, and control release properties can be obtained. The composition may be heated to temperatures of from about 40 to 200°C or higher, for from about 0.1 second to about 24 hours or longer. The composition is preferably heated to a temperature of from about 50 to 90°C for one second to one hour at an atmospheric pressure at sea level (about 760 mm Hg). Temperatures of 100°C or higher, formulated at atmospheric pressure at sea level (around 760 mm Hg), should be avoided if homogeneous, solid materials are desirable, as these high temperatures generally result in boiling, and disruption of the material. To achieve homogenous solid materials at these higher temperatures, the pressure during

formulation is preferably increased beyond atmospheric pressure at sea level (i.e. >760 mm Hg). At lower temperatures, solids can be produced at pressures below sea level, but the pressure should be sufficient to prevent boiling and disruption of the material. The amount of heat must generally be sufficient to change the physical state of the material. Through heating, the physical characteristics of the materials may be altered in a way that facilitates binding and/or entrapment of the drug, within the composition. In the following discussion and examples, the materials were formulated at the pressure at sea level (about 760 mm Hg) unless otherwise noted.

Further modulation of the state of the composition produced by heating can be achieved through the use of agitation or stirring during the heating process. The preparation of solids is best achieved by not stirring the composition during heating. Preparation of viscous, injectable compositions is best achieved by stirring the composition during the heating process, and maintaining the temperature at a level at which changes in the physical state of the composition first occurs. The temperature range at which the first changes occurs typically ranges from about 50 to 75°C, at which point the materials increase in thickness allowing control of the viscosity of the material. Higher temperatures tend to facilitate the formation of solids, even with stirring, and should be avoided if viscous, injectable materials are desired. On further heating, typically about 75 to 99°C, the materials increase in thickness and eventually form a solid or a material with a granular conformation.

For example, with the application of heat at atmospheric pressure at seal level (about 760 mm Hg) to compositions containing albumin as the first component without stirring, the material typically changes from a liquid to a gel or semi-solid, and then to a solid depending on the temperature. Generally, when the material is heated to about 65 to 70°C, the material can be formulated into a gel or semi-solid state. Once

the desired state is achieved, the composition must be removed from the heat, and cooled, to prevent its further solidification, and desiccation. On heating from about 70 to 99°C, albumin containing compositions tend to become a thick gel, and then a solid. The deformability, or softness, of the solid can generally be increased by increasing the concentration of the second component, and the rigidity of the composition can be increased by increasing the concentration of the first component.

Additionally, modulation of the second component in combination with albumin as the first component, can affect its physical characteristics. For example, the use of heparin results in a clear gel-like material, resembling gelatin. If hyaluronic acid is used, the material generally results in a white, opaque material, which resembles yogurt in consistency. Use of gelatin as the second component results in a white, opaque yogurt-like material while it is warm, and a gelatinous material when it is cooled.

When albumin is used as the first component, and the composition is stirred during heating, different physical properties can be achieved. Typically, temperatures of from about 65 to 70°C can be used to create a viscous solution if the material is cooled once the desired viscosity is achieved. If the composition is heated from about 70 to 99°C or higher the material becomes increasingly viscous, and rapidly solidifies into a thick, granular, and/or solid material. After stirring, one does not observe the smooth, homogenous solids typically seen when composition is prepared without stirring.

Another protein which can be used in a similar manner as a first component is fibrinogen. However, the temperature at which fibrinogen changes state tends to be lower than that of albumin, and the resulting material tends to be less firm, and more clot-like. Typically, without stirring, the material begins to solidify at about 60 to 65°C, and forms a solid from about 65 to 70°C or higher.

For drugs which are difficult to, or can not be, formulated into a solution but which must be used in a suspension, the use of heat to form a semi-solid or more viscous composition has particular additional advantages. Typically, formulations using these drugs must be vigorously mixed before use, because the drug tends to settle on the bottom of the container. However, by incorporating these drugs into a composition of the present invention, they can be evenly mixed at the time of manufacturing into the composition, "fixed" into place via the application of heat, and then distributed in an evenly distributed form, thereby eliminating the need for vigorous mixing before use.

When mixed with a dye, the composition can be solidified, and/or desiccated in situ for targeted drug delivery through the application of a matched laser wavelength. For example, a composition of: (1) hyaluronic acid, carboxymethylcellulose or hydroxypropylmethylcellulose; (2) albumin and/or fibrinogen; (3) a drug; and (4) indocyanine green dye, can be fixated to tissues in situ for targeted drug delivery through the application of diode laser energy (808 nm, 12 Watts/cm^2). Additional material containing the same or different drugs can be applied, and secured as needed. This allows the release of a combination of drugs to the site in a simultaneous or sequential manner depending on the mode of application and the components of the composition. Alternatively, a pocket can be filled with the preheated material, and the laser can be used to create a membrane over the material, thereby keeping the unheated drug and delivery vehicle localized to the cavity. This is advantageous for the targeted delivery of drugs whose parmacologic activity is reduced by the application of heat.

The physical state obtained by heating may range from substantially liquid form to a solid. The deformability, solidity and swell characteristics of the composition can be altered through a reduction in the water content of the composition. If a thin layer of the composition is partially or

completely dehydrated it forms a membrane-like material. The material can thus be formulated into a variety of shapes for application, for example, to open skin wounds, to form contact lenses for the release of drugs to treat eye diseases, as sheets for covering visceral organs and the like.

The formation of membranes or other viscous, semi-solid, or solid configurations can be achieved in a number of settings, either in situ or externally. In situ formation is achieved by applying the composition in its preheated state, and then applying the heat in situ. Examples of how this can be achieved are not limited and include the application of electrocautery, heat guns, heated probes, heated fluids, sound energy and/or energy in the form of electromagnetic radiation, such as monochromatic coherent light, monochromatic non-coherent light, polychromatic coherent light and polychromatic non-coherent light in a continuous or discontinuous manner. Examples of lasers which can be employed include Holmium:YAG (210 μm), thulium:YAG (2.06 μm) and Nd:YAG (1064 and 1320 μm), far infrared lasers such as the carbon dioxide laser (10,600 μm). Dye-laser combinations may also employed. The physical characteristics (i.e. viscosity; physical state - liquid, semi-solid, solid; elasticity; and flexibility) can be controlled through the amount of energy input, and the resulting amount of desiccation achieved. With increasing desiccation the material becomes stiff, and friable. With less desiccation, a more pliable material is formed. In this way, the composition can be applied in a targeted manner to tissues in which high concentrations of drugs are desired, such as infection sites (abscesses, corneal ulcers, etc.), to surgical sites using antibiotics (as prophylaxis to prevent infection), to tumor beds using antimetabolites, to graft sites using anticoagulants, as well as other applications.

For the in vitro production of membranes, a nonstick surface, such as polytetrafluroethylene (Teflon™), is preferred. For the formation of strong, tear resistant membranes at an

atmospheric pressure at sea level (about 760 mm Hg), the surface is generally heated at a pressure of about 760 mm Hg, to a temperature under about 100°C, preferably about 70°C, to prevent boiling and resulting hole or bubble formation in the material. The formulation of the composition under higher pressures or opposing plates, or a combination of higher temperatures with higher pressures, may further reduce hole formation and facilitate membrane formation. Temperatures under about 60 to 70°C tend to result in membranes with little or no tensile strength, which may be useful in certain applications.

The amount of desiccation can be controlled by the length of heating at a specific temperature, and is highly dependent on the thickness and amount of the material applied. Typically, to form desiccated membranes, which usually contain less than 10% water, heating is stopped when a thin, friable membrane is formed. After formation, the resulting membranes tend to absorb water, and become less friable, and better suited for application to an open skin wound, or as contact lenses. The drug component of the present invention may be added at this time.

Generally, the degree of swelling can be modulated by varying the concentrations of the components. Increasing the concentration of the second component, particularly proteoglycans and saccharides, typically increases the amount of swelling which occurs when the desiccated material is rehydrated. Increasing the concentration of the first component tends to decrease the amount of swelling which occurs on rehydration. The use of protein gel as the second component, also tends to reduce the amount of swelling which occurs after rehydration.

The production of the composition of the present invention may be performed in a number of ways, including, but not limited to the following preparation techniques, which generally result in a well formulated composition. For mixtures which do not form precipitates and do not separate over time: (1) Combine the components using the concentrations desired in a

sterile test tube or other sterile container. The drug may be added at this time or later, as for example the case of a desiccated membrane to which the drug may be added by placing the drug in an aqueous medium into which the desiccated membrane is placed for rehydration; (2) After combining the components, the composition should be gently agitated externally by shaking the container, or internally by stirring the composition using a spatula or other object which is inserted into the container. Both forms of agitation should be performed in a fashion which prevents the formation of bubbles, if a smooth, homogeneous material is desired; (3) After mixing, the material is optimally left standing, preferably in a refrigerator, generally for 1 hour or more, preferably 24 hours or more; (4) The material is then removed from the refrigerator and either heated externally or after implantation in situ to create the desired end product as previously described (IE viscous, semi-solid, membrane, etc.). (5) Preferably, if heated externally, the material is refrigerated at around 10°C after preparation.

For combinations in which the constituents form precipitates or do not form homogeneous solutions, even after agitation and the passage of time: (1) Combine the components, including the drug, using the concentrations desired in a sterile test tube or other sterile container; (2) After combining the components, the composition should be gently agitated externally, or internally stirred using a spatula or other object which is inserted into the composition. Both forms of agitation should be performed in a fashion which prevents the formation of bubbles, if a smooth, homogeneous material is desired; (3) The material should be promptly heated, to fix the drug into the material; (4) Preferably, if not heated in situ, the material is refrigerated at around 10°C.

For the production of homogeneous materials, gas bubble and/or vaporization bubble formation should be prevented. To achieve a homogeneous solution, the composition should not be heated at or to a temperature/pressure combination which exceeds

the boiling point of the composition. Boiling of the composition should be avoided. Typically, this is done by keeping the temperature below 100°C when the material is heated at ambient pressure at sea level (around 760 mm Hg), or by increasing ambient pressure if higher temperatures are desirable.

If gas/vaporization bubbles or holes are desired, as in the production of a sponge or porous material, they can be imparted into the composition before or during energy application in a number of fashions. These include, but are not limited to, lowering the pressure and/or increasing the temperature to a combination which exceeds the boiling point of the composition, stirring or agitating the composition vigorously to facilitate air bubble entrapment within the composition, injecting gas or air into the composition, using the venturi principle to incorporate gas or air into the compositions as it passed through tubing during the production process, by percolating gas or air into the composition, and/or by adding an additional agent to the composition which results in gas or vapor formation at a temperature below the boiling point of the composition much the way yeast when added to bread results in gas formation and the production of porous bread.

The composition may also include buffers to maintain the pH of the materials in a physiologically compatible range. Buffer which may be used include, but are not limited to, phosphate buffers and acetate buffers. Stabilizing agents such as methyl or propyl paraben may also be added, each in an amount of from about 0.001 to 20% by weight 0.01 to 15% by weight.

EXAMPLE I

0.40 ml of a 25% solution of human albumin obtained from the New York Blood Center was combined with 0.80 ml of sodium hyaluronate (Healon™ manufactured by Pharmacia, Inc.) and mixed in a sterile 10 ml red top Vacutainer™ (manufactured by Becton Dickinson) under vacuum conditions normally present in the

tube. 0.50 cc (20 mg) of a gentamicin solution was added to the container and allowed to settle for 2 days in a refrigerator at 10°C after thorough homogenization.

The mixture was heated to a temperature of from 68 to 72°C for 10 minutes in a temperature controlled water bath. The heated sample showed some turbidity compared with an unheated sample. The sample was removed from the tube and layered onto the bottom of a test chamber maintained at 22°C. 30 cc of 0.9% saline was added as a layer on top of the sample layer. At regular time intervals (4 hours, 8 hours and 24 hours) 2.5 ml samples were obtained from the mid portion of the chamber and the gentamicin levels in the samples measured. The results are shown in Table 1.

Two control samples A and B containing only albumin and gentamicin and hyaluronic acid and gentamicin, respectively in the amounts described above were heat treated in the same manner as Example 1. The results are shown in Table 1.

TABLE 1

SAMPLE	TIME INTERVAL	GENTAMICIN LEVELS (ug/ml)
SAMPLE 1	4 HOURS	8.3
CONTROL A	4 HOURS	26.7
CONTROL B	4 HOURS	22.1
SAMPLE 1	8 HOURS	21.5
CONTROL A	8 HOURS	29.8
CONTROL B	8 HOURS	33.5
SAMPLE 1	24 HOURS	29.9
CONTROL A	24 HOURS	38.3
CONTROL B	24 HOURS	36.9

As shown in Table 1 the composition of the present invention provided a controlled rate of delivery of gentamicin over 24 hours. Albumin alone and Healon alone (Controls A&B) showed early release of a major portion of the gentamicin making these samples unsuitable for the controlled release of the drug.

EXAMPLE 2

The experiment described in Example 1 was repeated except that the materials were heated for 10 minutes in a temperature controlled water bath maintained at 98-100°C. The results are shown in Table 2.

TABLE 2

SAMPLE	TIME INTERVAL	GENTAMICIN LEVEL (ug/ml)
SAMPLE 2	4 HOURS	8.52
SAMPLE 2	8 HOURS	13.1
SAMPLE 2	24 HOURS	16.8

The results shown in Table 2 indicate clearly that the composition of the invention shows controlled release of the drug. It should be noted that heating the composition to 100°C provided a slower release of the drug during the 24 hour test period as compared with Example 1.

EXAMPLE 3

3 ml of a 25% solution of human albumin (NYBCEN™, New York Blood Center, Inc.) was combined with 3 ml of sodium hyaluronate (Healon™, Pharmacia, Inc.), in a sterile 10 ml sterile red top Vacutainer™ under vacuum conditions normally present in the tube. 2.0 cc (80 mg) of gentamicin (Garamycin™, Schering Pharmaceutical Corporation) was added to the container. The combination was then shaken for 5 minutes until the mixture, which did not readily combine, was substantially homogenized. For further homogenization, the material was placed into a refrigerator and kept at 10°C for 2 days.

The materials were heated for a minimum of 5 minutes in a temperature controlled water bath maintained at 98-100°C. The heated materials showed considerable turbidity, and resembled yogurt in both color and texture.

Sprague-Dawley rats received 2.0 ml subcutaneous dorsal (back) injections of the composition containing 10 mg/ml gentamicin. The test animals were sacrificed at 4, 12, 14 and 48 hours. The implant material was surgically removed and was subjected to bacterial zone of inhibition studies.

Zone of inhibition studies indicate the amount of bacterial growth that occurs around the test material. A fixed volume of material is placed on a uniform lawn of bacteria in a culture medium and incubated for a fixed period of time. In this test, E. Coli sensitive to gentamicin were used for a period of 24 hour incubation. The results are reported as a ratio of the diameter of the zone of inhibition of bacterial growth over the diameter of the material being tested. Saline controls showed no evidence of inhibition of bacterial growth.

Serum gentamicin levels were determined for all specimens, and were adjusted for the weight of the animals. Relative extrapolated to a standard 300 gram rat are reported. Zone of inhibition studies were performed on residual implant material harvested at 4 and 48 hours. The results are shown in Table 3.

Control samples A, B, C, and D were evaluated in a similar manner to Example 3. Control sample A contained a combination of 6 cc of normal saline, and 2 cc of a 40 mg/ml solution of gentamicin (Garamycin™). Control sample B contained 3 cc of 25% human albumin and 3 cc of 0.9% saline with 2 cc of a 40 mg/ml solution of gentamicin (Garamycin™). Control sample C contained 2 cc of 10mg/ml hyaluronic acid (Healon™), 4 cc of normal saline, and 2 cc of a 40mg/ml solution of gentamicin (Geramycin™). Control Sample D was made by mixing 3.0 ml or a 25% solution of human albumin (NYBCEN) with 3.0 ml of sodium hyaluronate (Healon™), with 2.0 ml (80 mg) of gentamicin

(Garamycin™).

Samples A-D were then shaken for 5 minutes until they were substantially homogenized. For further homogenization, samples A-D were placed into a refrigerator and kept at 10°C for 2 days.

Samples A-D were heated for a minimum of 5 minutes in a temperature controlled water bath maintained at 98-100°C. After heating, the samples were refrigerated for 14 days at 10°C prior to evaluation in a similar fashion as example 3. The results are shown in Table 3.

TABLE 3

SAMPLE	TIME INTERVAL	IMPLANT MATERIAL HARVESTED APPROX VOLUME (ml)	SERUM GENTAMICIN LEVEL (μg/ml)	SERUM GENTAMICIN LEVEL (300 g STANDARD RAT) ug/ml	ZONE OF INHIBITION IMPLANT MATERIAL
SAMPLE 3	4 Hours	1.75	17.8	16.0	2.0
Control A	4 Hours	0	16.2	14.7	*
Control B	4 Hours	0	15.8	15.2	*
Control C	4 Hours	.25	15.9	14.8	2.1
Control D	4 Hours	0	6.5	5.7	*
SAMPLE 3	12 Hours	1.5	4.1	3.9	NT
Control A	12 Hours	0	<0.3	<0.3	*
Control B	12 Hours	0	0.4	0.4	*
Control C	12 Hours	0	<0.3	<0.3	*
Control D	12 Hours	0	<0.3	<0.3	*

SAMPLE 3	24 Hours	1.5	0.4	0.4	NT
Control A	24 Hours	0	<0.3	<0.3	*
Control B	24 Hours	0	<0.3	<0.3	*
Control C	24 Hours	0	<0.3	<0.3	*
Control D	24 Hours	0	<0.3	<0.3	*
SAMPLE 3	48 Hours	1	<0.3	<0.3	1.4
Control A	48 Hours	0	<0.3	<0.3	*
Control B	48 Hours	0	<0.3	<0.3	*
Control C	48 Hours	0	<0.3	<0.3	*
Control D	48 Hours	0	<0.3	<0.3	*

***** **No residual material in the test animal**
NT **Not tested**
<0.3 **Means below the threshold of detection**

As shown in Table 3 the composition of the present invention provided systemic delivery of gentamicin producing measurable levels over 24 hours. Albumin alone, Healon alone, and saline alone showed similar levels at 4 hours, but rapidly declined thereafter making these samples unsuitable for the controlled release of the drug. A combination of Healon, albumin, and gentamicin without heating showed a delay in the release of drug, with a measurable blood level at 12 hours, but did not maintain measurable blood levels for the same length of time as the composition of Sample 3, and is less suited for the controlled release of the drug than the composition of the present invention.

The presence of the composition of the present invention at the site of implantation at the 4, 12, 24, and 48 harvest times indicates the material is well suited for the controlled release and targeted delivery of drugs. The ability of Sample 3 to retain gentamicin for at least 48 hours is demonstrated by the ability of the implant material which was surgically removed at 48 hours to inhibit bacterial growth.

EXAMPLES 4-5

1.0 ml of a 25% solution of human albumin (NYBCEN) containing 10 mg/ml of indocyanine green dye (Cardio-Green™, Becton-Dickinson) was combined with 2.0 ml of sodium hyaluronate (Healon™), in a sterile 10 ml sterile red top Vacutainer™, under vacuum conditions normally present in the tube. 1.0 cc (40 mg) of gentamicin (Garamycin™) was added to the container. The combination was then shaken for 5 minutes until the mixture was largely homogenized. For further homogenization, the material was placed in a refrigerator and kept at 10°C for 2 days.

A small amount of the composition was placed in the bottom of a 1 cm diameter cylindrical metal container. A Coherent 810 Diode laser emitting at 810 mm, power 0.5 Watts, for

1.0 second duration, at a pulse interval of 0.2 seconds, through an Acculite™ Endoprobe Delivery System, resulting in a 2.0 mm spot size, and a power density of 15.9 Watts/cm^2, was then applied to the material. As the laser energy was applied, the composition was made into a partially desiccated, semi-solid, membranous material. After the contents of the container were treated, additional composition material was added and treated in a similar manner, until a total of 2 ml of the composition had been added. The endpoint was the production of a semi-solid material rather than total solidification and desiccation of the material. Two samples (Samples 4 and 5) were formulated, each composed of 2 ml of the composition.

Two Sprague-Dawley rats underwent surgical implantation of half of each sample (10mg Gentamicin) into a subcutaneous pocket. The pocket was created using a scalpel, and was closed using staples. Sacrifice and harvesting took place at 4 for the first test animal (Sample 4) and 12 hours for the second rat (Sample 5), with harvesting of serum, remaining composition, and overlying skin. Gentamicin levels in the serum were determined, and zone of inhibition studies were performed on the overlying skin and remaining composition material in a similar manner to that described in Example 3. The results are shown in Table 4.

TABLE 4

COMPOSITION	TIME INTERVAL	IMPLANT MATERIAL HARVESTED APPROX VOLUME (ml)	SERUM GENTAMICIN LEVEL (μg/ml)	SERUM GENTAMICIN LEVEL (300 g STANDARD RAT) ug/ml	ZONE OF INHIBITION IMPLANT
Sample 4	4 Hours	0.30	6.3	5.7	1.80
Sample 5	12 Hours	0.10	<0.3	<0.3	1.43

As shown in Table 4, the application of laser energy to the drug delivery composition does not destroy the activity of the drug located with in it.

EXAMPLE 6

A composition was formulated in the same manner as Example 5, and then applied to a pocket formed in freshly harvested rat skin. Laser energy was then applied in a similar manner as in Example 5, and a membrane was formed over the material located in the pocket of skin. On inversion of the skin the material remained in place. On irrigation of the skin with saline, and 5% human albumin, the material remained in place. In a similar fashion, when no laser energy was applied to the skin, irrigation with saline and or blood products such as albumin, resulted in the material being washed off of the skin surface.

EXAMPLE 7

The following examples (Examples 7-50) were each individually formulated in a sterile 10 ml sterile red top Vacutainer™. The 25% human albumin used in the examples was obtained from the New York Blood Center, Inc. The 12.5% fibrinogen was formulated by mixing 0.25 grams of desiccated fibrinogen (Desiccated Fraction 1, Type I-S, from bovine plasma, 80% clottable protein, Sigma™) with 2 ml of sterile water. The fibrinogen mixture was shaken for 5 minutes, to facilitate dissolution. The resultant mixture was turbid, resembling diluted skim milk, and some undissolved clumps were present on the walls of the tube. After refrigeration for 2 or more days, the clumps of material typically dissolved.

After formulation, the examples and controls were shaken until the component materials were dissolved, or a

homogenous mixture of the materials was obtained, or the time period exceeded 5 minutes. To determine the stability of the formulations, and to allow for further homogenization, the materials were placed into a refrigerator maintained at 10°C for at least 2 days. Before and after refrigeration, the samples were evaluated for there relative viscosity, the presence of precipitates, the distribution of the components of the composition, separation of the components, and clarity. Clarity was measured on a scale of 0 to 3, with 0 being as clear as water, and 3 being a turbid solution similar to 2% low fat milk. Relative viscosity was measured on a scale of 1 to 10 with 1 being the relative viscosity of water, and 10 being equivalent to 1% sodium hyaluronate (Healon™) at rest.

The samples were heated for a minimum of five minutes in a temperature controlled water bath which was maintained at 98-100°C at atmospheric pressure at sea level (around 760 mm Hg). Before heating the compositions, if there was evidence of separation or precipitation, the composition was shaken for 5 minutes until homogenized. After heating, the physical state of the material (solid, semi-solid, liquid), its color, the presence of free liquid, and the handling characteristics were determined.

After heating, the materials were refrigerated for a minimum of 48 hours and were observed for the changes noted above. In the absence of free water, none of the materials whether in the form of solids, semisolids, or viscous solutions showed evidence of separation, change in color, or change in state after the 48 hour time period.

0.6 ml of a 25% solution of human albumin with 0.5 ml of sodium hyaluronate (Healon™, Pharmacia Inc.), were combined with 0.90 ml (36 mg) of gentamicin (Garamycin™, Schering Pharmaceutical Corporation, Manati, Puerto Rico).

Control Sample A was made by combining 3.0 ml of a 25% solution of human albumin with 1.0 ml (40 mg) of gentamicin (Garamycin™). Control Sample B was made by combining 0.6 ml of

a 25% solution of human albumin with 0.5 ml of sterile water and 0.9 ml (36 mg) of gentamicin (Garamycin™). Control Sample C was made by combining 0.5 ml of sodium hyaluronate (Healon™) with 0.5 ml (10 mg) of gentamicin (Garamycin™). The results are shown in Table 5.

TABLE 5

Pre Heating					After Heating
Composition	Viscosity (1-10)	Clarity (0-3)	Description	State	Description
Sample 7	3	0	Homogeneous	Semi-Solid	White, yogurt like consistency. Does not readily dissolve in H_2O. No free fluid in test tube.
Control A	1	0	Homogeneous	Solid	White, solid Swiss cheese consistency. Cylindrical plug, resists deformation 75% solid, 25% liquid.
Control B	2	0	Homogeneous	Solid	While, solid material similar to A, but smaller cylinder 36% solid, 64% liquid.
Control C	6	0	Homogeneous	Liquid	Same as preheated state

Example 7 demonstrates that the composition of the present invention produces a homogenous, injectable material. Controls A and B formed a solid white, plug with a large amount of free fluid, that is undesirable for drug delivery. Control sample C showed no change in state,and a hyaluronic acid/drug combination is known to be a poor drug delivery composition.

EXAMPLES 8-12

Sample 8 was made by combining 0.4 ml of a 25% solution of human albumin with 0.25 ml of Heparin (10,000 units/ml, Wyeth Laboratories Inc., Philadelphia, PA). Sample 9 was made by combining 0.4 ml of a 25% solution of human albumin with 0.4 ml of sterile water and 0.25 ml of Heparin (10,000 units/ml, Wyeth Laboratories Inc.) Sample 10 was made by combining 0.4 ml of a 25% solution of human albumin with 0.4 ml 2% hydroxypropylmethylcellulose (Occucoat™, Storz) and 0.25 Heparin (10,000 units/ml, Wyeth Laboratories Inc.). Sample 11 was made by combining 0.4 ml of a 25% solution of human albumin with 0.25 ml Heparin (10,000 units/ml, Wyeth Laboratories Inc.), and 0.4 ml (8 mg) of gentamicin (Garamycin™). Sample 12 was made by combining 0.4 ml of a 25% solution of human albumin with 0.25 ml Heparin (10,000 units/ml, Wyeth Laboratories Inc.) and 0.4 ml (20 mg) of Fluorouracil (Hoffmann-LaRoche, Inc., Nutley NJ).

Control Sample A was made by combining 0.25 ml of Heparin (10,000 units/ml, Wyeth Laboratories Inc.) with 0.4 ml of water, and 0.4 ml (20 mg) of Fluorouracil (Hoffmann-LaRoche, Inc., Nutley, NJ).

Control Sample B was made by combining 0.4 ml 2% hydroxypropylmethylcellulose (Occucoat™, Storz) with 0.25 ml of Heparin (10,000 units/ml, Wyeth Laboratories Inc.). The results are shown in Table 6.

TABLE 6

PRE-HEATING				AFTER HEATING	
Composition	Viscosity (1-10)	Clarity (0-3)	Description	State	Description
Sample 8	1	0	Yellow tint Homogeneous	Solid	Clear, Yellow tint, Gelatin like, Clean fracture planes, Cylindrical plug, resists deformation, No free fluid in test tube, Firmer than Example 9
Sample 9	1	0	Yellow tint Homogeneous	Solid	Clear, Yellow tint, Gelatin like, Similar to Example A, but not as firm, No free fluid in test tube liquid
Sample 10	3	0	Yellow tint Homogeneous	Semi-Solid	Cloudy +2, Gelatin like, but more slippery than Control A or B, Does not readily dissolve in H_2O, No free fluid in test tube
Sample 11	1	1	White precipitation on the bottom	Solid	White, Solid, Cylinder, Similar to albumin, 38% free milky white water

Sample 12	1	0	Yellow tint Homogeneous	Solid	Cloudy +2, white-grey like color, Gelatin like consistency
Control A	1	0	Yellow tint Homogeneous	Liquid	Clear fluid, No change in physical state
Control B	6	0	Homogeneous	Solid	After cooling, forms clear liquid, with similar viscosity as pre-heated state, Solid precipitate forms while hot, with free water content of 92%. Dissolves after cooling.

Samples 8 and 9 demonstrate that by altering the albumin concentration, the degree of gelling can be changed in a controlled manner. As the concentration of albumin increases, the resulting material becomes more solid or gel-like. Sample 10 shows that a mixture of one protein (albumin), plus two second components (hydroxypropylmethycellulose[HPMC] and heparin), forms a gelatinous, material. As compared to a combination of albumin and heparin, the addition of HPMC makes the material more slippery, a property which may be useful for certain applications such as injection. Sample 12 shows a drug delivery formulation of a human albumin/heparin combination, in which the drug, fluorouracil, does not precipitate out of solution.

Controls A and B show that without the presence of the first component of the present invention, a peptide, a permanent change in the physical state of the composition does not occur.

EXAMPLE 13

Sample 13 was prepared in a like manner to Sample 8. A temperature probe was inserted into the center of the test tube, and was employed to monitor the temperature of the composition, while under stirring. The material was then heated in a 98-100°C water bath. Changes in the physical state, viscosity, and color of the composition were noted, as were the temperatures at which these changed occurred.

As the temperature of the material rose from 30°C to 65°C, there was little change in the clear, yellow contents of the tube. From 65°C to 70°C, the contents became slightly cloudy, +1 on the aforementioned scale, with a grey-white tint. At 70°C the contents became viscous, but not solid in nature. The material was removed from the water bath, and allowed to cool. The resulting material was a homogeneous, viscous, and tenacious.

The tube was then returned to the water bath. As the temperature of the mixture rose from 70°C to 80°C, the material changed from a tenacious, viscous fluid, into a solid, chunky, gelatinous material. It remained slightly cloudy, with a grey-white color, similar to skim milk. As the temperature was further increased to 100°C, no further change occurred.

Control A was prepared with 0.65 ml of 25% human albumin. As the temperature of the material rose from 30°C to 65°C, there was little change in the clear, yellow contents of the tube. From 65°C to 70°C, the contents became a turbid, yellow-white color. From 70°C to 80°C, the contents became whiter, and more viscous, but not solid. Form 80°C to 100°C, the material continued to solidify, becoming a very thick, tenacious material which had a dry, gritty consistency resembling cream of wheat. The resulting white material was neither slippery nor sticky.

Control B contained 0.5 ml of Heparin (10,000 units/ml, Wyeth Laboratories Inc., Philadelphia, PA) alone and was treated in the same manner as Control A. As the temperature increased from 30 to 100°C, there was no change in the physical state, color or viscosity of the material.

Example 13 demonstrates that by controlling the temperature and by stirring the components of the present invention during the heating process, further modulation of the physical state of the material can be achieved.

EXAMPLES 14-16

Sample 14 was made by combining 0.5 ml of a 12.5% solution of fibrinogen with 0.5 ml of a 2% hydroxyproplymethylcellulose (Occucoat™, Storz) and 0.25 ml Heparin (10,000 units/ml, Wyeth Laboratories Inc.). Sample 15 was made by combining 0.5 ml of 12.5% solution of fibrinogen with 0.25 ml Heparin (10,000 units/ml, Wyeth Laboratories Inc.). Sample 16 was made by combining 0.2 ml of a 12.5% solution of fibrinogen with 0.2 ml sterile water, and 0.25 ml Heparin (10,000 units/ml, Wyeth Laboratories, Inc.).

Control Sample A was made by combining 0.5 ml of a 12.5% solution of fibrinogen with 0.5 ml sterile water. The results are shown in Table 7.

TABLE 7

Composition	Viscosity (1-10)	Description	State	Description
Sample 14	4	Cloudy +1 Homogeneous	Solid	White, clot like mass 48% free white water, Adhesivity of clot similar to plain fibrin
Sample 15	1	Cloudy +1 Homogeneous	Solid	White, Homogeneous, Egg white like mass, Resists deformation, 13% clear fluid, Resists tearing more than fibrinogen alone
Sample 16	2	Clear Homogeneous	Liquid Homogeneous	White, Highly viscous, mucinous, stringy, Not a solid like A, No free water, just viscous material
Control A	1	Cloudy +1 Homogeneous	Solid	White mass, similar to egg white, more friable, more deformable, more clot like, than example 15

Samples 15 and 16 show that modulation of the fibrinogen concentration, through dilution with water, can be used to control the physical state of the resultant solution. Control sample A shows that heating fibrinogen alone changes the physical state of the material, but in a different fashion compared to that of the present invention.

EXAMPLES 17-25

Sample 17 was made by combining 0.2 ml of a 25% solution of human albumin with 0.2 ml of 1% sodium hyaluronate (Amvisc™, MedChem Products, Inc., Woburn, MA), and 0.1 ml of ampicillin 250 mg/ml (Mfd. For Elkins-Sinn, Inc., Cherry Hill, N.J.). Sample 18 was made by combining 0.2 ml of a 25% solution of human albumin with 0.2 ml of 1% sodium hyaluronate (Amvisc™) and 0.1 ml of cefazolin 330 mg/ml (Schein Pharmaceutical, Inc., Port Washington, NY). Sample 19 was made by combining 0.2 ml of a 25% solution of human albumin with 0.2 ml of 1% sodium hyaluronate (Amvisc™), and 0.1 ml of Fluorouracil 500 mg/ml (Hoffmann-LaRoache Inc., Nutley, NJ). Sample 20 was made by combining 0.2 ml of a 25% solution of human albumin with 0.2 ml of 1% sodium hyaluronate (Amvisc™), and 0.1 ml of Betamethasone Sodium 4mg/ml (Schein Pharmaceutical, Inc. Port Washington, NY).

Sample 21 was made by combining 0.2 ml of a 12.5% solution of fibrinogen with 0.2 ml of 1% sodium hyaluronate (Amvisc™), and 0.1 ml of ampicillin 250 mg/ml. Sample 22 was made by combining 0.2 ml of 12.5% solution of fibrinogen with 0.2 ml of 1% sodium hyaluronate (Amvisc™), and 0.1 ml of cefazolin 330 mg/ml (Schein Pharmaceutical, Inc.). Sample 23 was made by combining 0.2 ml of a 12.5% solution of fibrinogen with 0.2 ml of 1% sodium hyaluronate (Amvisc™), and 0.1 ml of Fluorouracil 500 mg/ml (Hoffmann-LaRoache Inc., Nutley, NJ). Sample 24 was made by combining 0.2 ml of a 12.5% solution of fibrinogen 25% solution of human albumin with 0.2 ml of 1% sodium hyaluronate (Amvisc™) and 0.1 ml of Betamethasone Sodium 4 mg/ml. Sample 25

was made by combining 0.2 ml of 12.5% solution of fibrinogen with 0.2 ml of 1% sodium hyaluronate (Amvisc™), and 0.1 ml of Betamethasone Sodium 4 mg/ml. The results are shown in Table 8.

TABLE 8

	PRE-HEATING			AFTER HEATING	
Composition	Viscosity (1-10)	Description	State	Description
Sample 17	5	Clear Homogeneous	Solid	Cloudy +1, grey- white like color very firm, disc like mass, No free water, Adhesivity of clot similar to plain fibrin
Sample 18	5	Clear Homogeneous	Solid	Cloudy +2, Whitish/Yellow mass, similar to Example 17, but not as firm, No free water
Sample 19	5	Clear Homogeneous	Semi-Solid	Cloudy +2, Milky Yellow-white color, more custard like consistency, No free water
Sample 20	5	Clear Homogeneous	Semi-Solid	White, custard like, No free water
Sample 21	5	Separation Cloudy 1 top, clear bottom 10%	Semi-Solid	White, More stringy like vitreous or nasal secretions or a blood cot No free water
Sample 22	5	Separation Cloudy 1 top, clear bottom 10%	Semi-Solid	White, More stringy like vitreous or nasal secretions or a blood clot No free water

Sample 23	5	Separation Cloudy 1 top, clear bottom 10%	Semi-Solid	White, More stringy like vitreous or nasal secretions or a blood clot No free water
Sample 24	5	White precipitate	Semi-Solid	White, More stringy like vitreous or nasal secretions or a blood clot No free water

Examples 17-25 demonstrate that the composition of the present invention can be formulated using a number of different drugs, as, for example, the combination of albumin and fibrinogen as the first component, and hyaluronic acid as the second component, in a manner that results in the desired physical changes upon the application of heat.

EXAMPLES 26-31

A 2% alginic acid was made by mixing 0.2 grams of alginic acid (Alginic Acid sodium salt, High Viscosity, Sigma™, St. Louis, Mo) with 10 ml sterile water. Dissolving the alginic acid was difficult despite vigorous shaking for 5 minutes. The specimen was heated to 98-100°C, with a small improvement in the solubilization of the material, but no change in its physical state. The resulting material was clear viscous and had a light yellow tint. The viscosity of the 2% alginic acid without additional components was 10+.

Sample 26 was made by combining 0.5 ml of a 25% solution of human albumin with 0.5 ml of the 2% alginic acid product.

Sample 27 was made by combining 0.5 ml of a 25% solution of human albumin with 0.5 ml of the 2% alginic acid product, and 0.5 ml (10 mg) of gentamicin (Garamycin™).

Sample 28 was made by combining 0.5 ml of a 12.5% solution of fibrinogen with 0.5 ml of the 2% alginic acid product.

Sample 29 was made by combining 0.5 ml of a 12.5% solution of fibrinogen with 0.5 ml of the 2% alginic acid product, and 0.5 ml (10 mg) of gentamicin (Garamycin™).

Sample 30 was made by combining 0.5 ml of a 12.5% solution of fibrinogen with 0.5 ml of the 2% alginic acid product, and 0.5 ml (125 mg) of Ampicillin (Mfd. for Elkins-Sinn, Inc. Cherry Hill, N.J.)

Sample 31 was made by combining 0.25 ml of a 25% solution of human albumin with 1.0 ml of a 2% alginic acid product.

Sample 32 was made by combining 1.0 ml of a 25% solution of human albumin with 0.25 ml of a 2% alginic acid product. The results are shown in Table 9.

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TABLE 9

PRE-HEATING				AFTER-HEATING	
Composition	Viscosity (1-10)	Clarity (0-3)	Description	State	Description
Sample 26	7	0	Homogeneous	Semi-Solid	White, yogurt like consistency, Does not readily dissolve in H_2O, No free fluid in test tube.
Sample 27	0	0 top Solid White on bottom	Separated Clear yellow on top, white precipitate on bottom, could not be stirred into a homogeneous material	Solid	White, solid mass, Cylindrical plug, resists deformation, Similar to 25% albumin, but no free water
Sample 28	7	0 top 1-2 bottom	Separated	Semi-Solid	White, but not as white as albumin, Tenacious, and stringy, but not slippery like Vitreous, Not slippery. No free water.

Sample 29	0	0 top White bottom	Separated Ball of sticky, very rough material on bottom could not be stirred into a homogeneous material	Solid-chunks	White, solid chunks in the bottom
Sample 30	3	Trace		Semi-Solid	Turbid, white gelatin like material, Resembles apple sauce in appearance Considerably more turbid and thicker than preheated
Sample 31	9	0	Homogeneous	Semi-Solid Liquid	White, but not as white as albumin, Thick, viscous 10+ material, Not slippery. No free water.
Sample 32	7	0	Homogeneous	Semi-Solid	White, but not as white as albumin, Comes out as chunks, Not slippery, No free water

Samples 27 and 29 show that some drug/polysaccharide/protein compositions are undesirable, as gentamicin caused precipitation of the alginic acid in these examples. However, sample 30 shows that other drugs can be combined and heated to form materials which have changes in the physical state desired for drug delivery compositions. Samples 26, 31 and 32 show that the handling characteristics can also be modulated through varying the concentrations of the components of the material.

EXAMPLE 33

Sample 33 was formulated in the same manner as Sample 26. A red topped tube was placed in a water bath maintained at 98-100°C. A temperature probe was placed into the center of the material in the test tube, and was used to stir the contents. As thee temperature of the material rose from 30°C to 65°C, there was little change in the clear, contents of the tube. From 65°C to 70°C, the contents became turbid. At 70°C, the contents became viscous, but not solid. The material was removed from the water bath, and allowed to cool. The resulting material had a thick, apple sauce like consistency, and a color similar to that of skim milk. The tube was then returned to the water bath. As the temperature of the mixture rose from 70°C to 80°C, the material became whiter and thicker, but did not turn into a solid.

EXAMPLE 34

Sample 34 was formulated in the same manner as Samples 26 and 33. The red topped tube was placed in water bath which was maintained at 98-100°C. A temperature probe was placed into the center of the material in the test tube, but in this example the sample temperature probe was not used to stir the contents of the test tube. As the temperature of the material rose from

30°C to 65°C, there was little change in the clear contents of the tube. From 65°C to 70°C, the contents became turbid. At 70°C, the contents formed a white mass with a custard like consistency. Further heating caused little, if any, change in the physical state.

EXAMPLES 35-39

1% Carboxymethylcellulose (CMC) was made by mixing 0.2 grams of CMC (Carboxymethylcellulose sodium salt, High Viscosity, Sigma™, St; Louis, MO) with 10 ml sterile water. Dissolving the CMC was difficult despite vigorous shaking for 5 minutes. After 1 hour, the remaining material dissolved. The resulting CMC product was used for Samples 35-39.

Sample 35 was made by combining 0.5 ml of a 25% solution of human albumin with 0.5 ml of the 1% CMC product.

Sample 36 was made by combining 0.5 ml of a 25% solution of human albumin with 0.5 ml of the 1% CMC product and 0.5 ml (10 mg) of gentamycin (Garamaycin™).

Sample 37 was made by combining 0.5 ml of a 12.5% solution of fibrinogen with 0.5 ml of the 1% CMC product.

Sample 38 was made by combining 0.5 ml of a 12.5% solution of fibrinogen with 0.5 ml of the 1% CMC product and 0.5 ml (10 mg) of gentamicin (Garamycin™).

Control A was made by mixing 0.5 ml of the 1% CMC product with 0.5 ml of sterile water.

A temperature probe was inserted into Samples 35-38 during heating. Samples 35 and 37 were not stirred, and Samples 36 and 38 were stirred. In Samples 35 and 37 whitening occurred around the side walls of the tube starting when the temperature at the center of the tube reached 40°C. In Sample 35, the central core whitened and solidified between 70-80°C, whereas in Sample 37 the central core whitened and solidified between 55-60°C. In Sample 36 and 38 whitening did not occur below 55°C, however in Sample 38 generalized whitening occurred between 55

to 70°C, whereas in example 36 whitening did not occur until 65 to 70°C. The material in Sample 38 formed a mass which adhered strongly to the probe. The results are shown in Table 10.

TABLE 10

PRE-HEATING				AFTER-HEATING	
Composition	Viscosity (1-10)	Clarity (0-3)	Description	State	Description
Sample 35	2	0	Homogeneous	Solid	White, egg white yogurt like consistency, fairly firm. No free fluid in test tube
Sample 36	1	0 top, 80% 1 bottom	Separated	Liquid	White, fluffy material,like curdled milk. Some free water, hard to measure
Sample 37	3	0 top, 75% 1-2 bottom	Separated Turbid material in bottom resembles 12.5% fibrin solution	Solid	White, clot like material Tenacious, and stringy, but not slippery like those containing hyaluronic acid, 10% free water
Sample 38	2	0 top 80% 1-2 bottom	Separated as with example 37	Solid	White, clot like mass similar to Example 37. 10% free water
Control A	3	0	Clear	Liquid	No change on heating

EXAMPLES 39-42

A 25% gelatin product was made by mixing 2.5 grams of Gelatin (Type B form bovine skin, Sigma™, St; Louis, MO) with 10 ml sterile water. To facilitate dissolving the gelatin, the red topped tube was heated in a 98-100°C water bath. After 30 minutes, the gelatin completely solubilized, forming a clear, yellow tinted, fluid. The resulting gelatin product was then cooled to 55°C, and used to formulate Samples 39-42. The gelatin was a liquid at this temperature, with a relative viscosity of 2. As the material was cooled further to a 10°, it formed a firm gel, with 10+ viscosity.

Sample 39 was made by combining 0.5 ml of a 25% solution of human albumin with 0.5 ml of the 25% gelatin product.

Sample 40 was made by combining 0.5 ml of a 25% solution of human albumin with 0.5 ml of the 25% gelatin product, and 0.5 ml (10 mg) of gentamicin (Garamycin™).

Sample 41 was made by combining 0.5 ml of a 12.5% solution of fibrinogen with 0.5 ml of the 25% gelatin product.

Sample 42 was made by combining 0.5 ml of a 12.5% solution of fibrinogen with 0.5 ml of the 25% gelatin product, and 0.5 ml (10 mg) of gentamicin (Garamycin™).

In Examples 39-41, the materials exhibited a custard-like consistency, but after cooling to 10°C, the material became more gelatinous, having the physical characteristics of gelatin. The results are shown in Table 11.

TABLE 11

PRE-HEATING				AFTER-HEATING	
Composition	Viscosity (1-10)	Clarity (0-3)	Description	State	Description
Sample 39	10	0	Homogeneous	Solid	White, custard like while hot. Formed, firm gelatinous material on cooling. No free fluid in test tube.
Sample 40	10	0	Homogeneous	Solid	White, custard like while hot. Formed, firm gelatinous material on cooling. No free fluid in test tube.
Sample 41	10	3+	Homogeneous	Solid	White, more stringy than example 37, formed, firm gelatinous material on cooling. No free fluid in test tube.
Sample 42	10	3+	Homogeneous	Solid	White, similar to example 38

EXAMPLE 43

Sample 43 was formulated in the same fashion as in Sample 40, but was stirred during heating. The resulting product had a granular, cream of wheat-like consistency, unlike the solid mass formed without stirring.

EXAMPLES 44-47

A 10% mucin product was made by mixing 0.2 grams of Mucin (Type II:Crude from porcine stomach, Sigma™, St; Louis, MO) with 10 ml sterile water in a 10 ml red topped tube. The mucin formed a turbid material, with little increase in viscosity by the addition of the water. The resulting material was a brown, turbid, liquid.

Sample 44 was made by combining 0.5 ml of a 25% solution of human albumin with 0.5 ml of the 10% mucin product.

Sample 45 was made by combining 0.5 ml of a 25% solution of human albumin with 0.5 ml of the 10% mucin product, and 0.5 ml (10 mg) of gentamicin (Garamycin™).

Sample 46 was made by combining 0.5 ml of a 12.5% solution of fibrinogen with 0.5 ml of the 10% mucin product.

Sample 47 was made by combining 0.5 ml of a 12.5 solution fibrinogen with 0.5 ml of the 10% mucin product, and 0.5 ml (10 mg) of getamicin (Garamycin™). The results are shown in Table 12.

TABLE 12

PRE-HEATING				AFTER-HEATING	
Composition	Viscosity (1-10)	Clarity (0-3)	Description	State	Description
Sample 44	2	3+	Homogenous, with some settling on bottom	Liquid	White, thick, slippery, material like Miracle Whip™ in consistency. No free fluid in test tube
Sample 45	2	3+	Homogeneous, with some settling on bottom	Semi-Solid	White similar to Example 42 but more clot like
Sample 46	2	3+	Homogeneous with some settling on bottom	Semi-Solid	White clot like similar to Example 42
Sample 47	2	3+	Homogenous with some settling on bottom	Fluid	White curdled milk appearance

EXAMPLE 48

Sample 48 was made by combining 0.8 ml of a 25% solution of human albumin (NYBCEN™, New York Blood Center, Inc.) with 0.8 ml of sodium hyaluronate (Healon™, Pharmacia Inc.), and 0.9 ml (36 mg) of gentamicin (Garamycin™).

The material was then placed on a Teflon frying pan at different temperatures, to determine the effect of heat on desiccation of the material at atmospheric pressure at sea level (around 760 mm Hg). At a temperature of 172°C, the material forms a ball of material, and rolls around on the surface of the frying pan. When it is placed on a frying pan at 70°C, the material starts to whiten, and, when maintained at 70°C forms, thin friable membranes. Placement of the material in water causes partial rehydration, and the strength and flexibility of the material returns. If heated to 100°C, the material boils, forming holes which is not desirable for forming sheets of the material. At temperatures below 70°C, first the edges become desiccated leaving a thick central portion, resembling a fried egg in configuration. When the material is placed in water, the membranes swell, and have little or no strength. When desiccated at a temperature of about 40°C, and then rehydrated, the material resumes a form similar to the preheated state.

EXAMPLES 49-52

The following materials were placed on a frying pan and heated to 70-80°C, until desiccation reached at least 90%

Sample 49 was made by mixing 1.0 ml of the 25% gelatin product described in Samples 39-42, and 1.0 ml of 25% human albumin to form a white, membranous material, which was extremely resistant to tearing. However, on placement of the material in water, it became very friable, greatly reducing its resistance to tearing. When incompletely desiccated, it became very sticky.

Sample 50 was made by mixing 0.4 ml of 25% human

albumin, with 0.4 ml of 12.5% fibrinogen and 0.8 ml of Amvisc™. The resulting material formed a thin membrane, which was relatively clear and brittle, after approximately 95% desiccation. On placement in water the material swelled, and became more flexible, while retaining some of its original strength.

Sample 51 was made by mixing 0.5 ml of 25% human albumin, with 0.5 ml of 12.5% fibrinogen. The was heated until it became a solid mass resembling egg white, but resisted tearing to a greater degree. The resulting material was thicker than pure albumin, had a relatively uniform thickness, and did not swell when water was added.

Sample 52 was made using only 25% human albumin. After heating, it had a fried egg appearance with thin friable edges and a thicker, tougher central portion. When the material was added to water it did not swell.

EXAMPLES 53-66

Sample 53 was formulated by mixing 1.0 ml of 2% hydroxypropylmethylcellulose (Occucoat™, Storz), with 0.75 ml of 12.5% fibrinogen, and 0.25 ml (10 mg) of gentamicin (Garamycin™).

Sample 54 was formulated by mixing 1.0 ml of 2% hydroxypropylmethylcellulose (Occucoat™, Storz), with 0.75 ml of 12.5% fibrinogen, and 0.25 ml (12.5 mg) of Fluorouracil™.

Sample 55 was formulated by mixing 1.0 ml of 1% carboxymethylcellulose, 0.75 ml of 12.5% fibrinogen, and 0.25 ml (10 mg) of gentamicin (Garamycin™).

Sample 56 was formulated by mixing 1.0 ml of 1% carboxymethylcellulose, 0.75 ml of 12.5% fibrinogen, and 0.25 ml (62.5 mg) of ampicillin.

Sample 57 was formulated by mixing 1.0 ml of 1% carboxymethylcellulose, 0.75 ml of 12.5% fibrinogen, and 0.25 ml (12.5 mg) of Fluorouracil™.

Sample 58 was formulated by mixing 1.0 ml of 2% hydroxypropylmethylcellulose (Occucoat™, Storz), 0.375 ml of 12.5% fibrinogen, 0.375 ml of 25% human albumin, and 0.25 ml (10 mg) of gentamicin (Garamycin™).

Sample 59 was formulated by mixing 1.0 ml of 2% hydroxypropylmethylcellulose (Occucoat™, Storz), 0.375 ml of 12.5% fibrinogen, 0.375 ml of 25% human albumin, and 0.25 ml (12.5 mg) of Fluorouracil™.

Sample 60 was formulated by mixing 1.0 ml of 1% carboxymethylcellulose, 0.375 ml of 12.5% fibrinogen, 0.375 ml of 25% human albumin, and 0.25 ml (10 mg) of gentamicin (Garamycin™).

Sample 61 was formulated by mixing 1.0 ml of 1% carboxymethylcellulose, 0.375 ml of 12.5% fibrinogen, 0.375 ml of 25% human albumin, and 0.25 ml (12.5 mg) of Fluorouracil™.

Sample 62 was formulated by mixing 1.0 ml of 2% hydroxypropylmethylcellulose (Occucoat™, Storz), 0.75 ml of 25% human albumin, and 0.25 ml (10 mg) of gentamicin (Garamycin™).

Sample 63 was formulated by mixing 1.0 ml of 1% carboxymethylcellulose, 0.75 ml of 25% human albumin, and 0.25 ml (10 mg) of gentamicin (Garamycin™).

Sample 64 was formulated by mixing 1.0 ml of hyaluronic acid/chondroitin sulfate mixture (Viscoat™, Alcon) with 0.375 ml of 12.5% fibrinogen, 0.375 ml of 25% human albumin, and 0.25 ml (12.5 mg) of Fluorouracil™)

Sample 65 was formulated by mixing 0.5 ml of 12.5% fibrinogen, 0.5 ml of 25% human albumin, and 0.25 ml (12.5 mg) of Fluorouracil™.

Sample 66 was formulated by mixing 1.0 ml of carboxymethylcellulose, 0.375 ml of 12.5% fibrinogen, 0.375 ml of 25% human albumin, and 0.25 ml (62.5 mg) of ampicillin.

After formulation, 0.01-0.05 ml of each composition was placed on excised rat skin. Laser energy was applied using a Coherent 810 Diode laser emitting 300 mW, for 1.0 second duration, at a repetition rate of 0.2 seconds through a Acculite™ Endoprobe Delivery System with a spot size of 2 mm. The energy density was 10 Watt/cm^2. Laser energy was applied to the material for a time period sufficient to cause it to "harden", and adhere to the skin, and deliver the drug in a localized, targeted fashion. 3 ml of normal saline was irrigated over the "hardened" material in an attempt to wash the composition off the skin, and its ability to resist fluid irrigation was recorded. The strength of adhesion was then qualitatively determined on a scale of 1-10, where 1 indicated no adhesion, and 10 indicated strong adhesion. The results are shown in Table 13.

TABLE 13

EXAMPLE	VISCOSITY (1-10)	COLOR	RESISTANCE TO SALINE IRRIGATION	ADHESION	DIFFICULTY WIPING OFF
Sample 53	4	Whitish green	Yes	5	Easy
Sample 54	4	Dark green	No	5	Easy
Sample 55	4		No	1	Easy
Sample 56	6	Darker	Yes	8	Hard
Sample 57	4	Darker	Yes	8	Hard
Sample 58	4	White	No	6	Medium
Sample 59	4	Dark	Yes	8	Hard
Sample 60	2	Dark	Yes	8	Hard
Sample 61	7	White	Yes	6	Hard
Sample 62	2	White	Yes	6	Hard
Sample 63	2	Dark	No	4	Easy
Sample 64	9	Dark	No	5	Easy
Sample 65	2	Dark	No	4	Easy
Sample 66	7	Dark	Yes	7	Hard

WHAT WE CLAIM IS:

1. A drug delivery composition comprising:

(a) at least one first component selected from natural or synthetic peptides, derivatives or variants of said natural or synthetic peptides or mixtures thereof;

(b) at least one second component adapted to support the first component upon the application of energy to the composition; and

(c) at least one drug.

2. The composition of Claim 1 wherein the peptides are selected from structural proteins, serum proteins or mixtures thereof.

3. The composition of Claim 2 wherein the proteins are selected from collagen, albumin, α-globulins, ß-globulins, -globulins, transthyretin, elastin, fibronectin, fibrinogen, fibrin or thrombin, or mixtures thereof.

4. The composition of Claim 1 wherein the amount of the first component is in the range of from about 0.1 to 95% by weight.

5. The composition of Claim 4 wherein the amount of the first component is from about 1 to 35% by weight.

6. The composition of Claim 1 wherein the second component is selected from proteoglycans, glycoproteins, protein gels, gelatins, saccharides, polyalcohols, natural or synthetic derivatives thereof, enzymatically cleaved or shortened variants, salts, cross-linked, oxidized or hydrolyzed derivatives or subunits thereof, and mixtures thereof.

7. The composition of Claim 6 wherein the proteoglycans are selected from natural or synthetic non-cellular body matrix materials found in the interstices between cells.

8. The composition of Claim 7 wherein said body matrix materials are selected from hyaluronic acid, salts of hyaluronic acid, chondroitin sulfate, dermatin sulfate, keratin sulfate, heparin, and heparin sulfate.

9. The composition of Claim 7 wherein the protein gel

is selected from collagen, caseinates, fibrin or fibrinogen.

10. The composition of Claim 7 wherein the gelatin is elastin.

11. The composition of Claim 7 wherein the saccharides are selected from fructose, hydroxypropylmethylcellulose, carboxymethylcellulose, dextrans, agarose, alginic acid or pectins.

12. The composition of Claim 7 wherein the polyalcohol is selected from glycerine, mannitol or sorbitol.

13. The composition of Claim 6 wherein the amount of proteoglycans is in the range of about 0.01 to 75% by weight.

14. The composition of Claim 6 wherein the amount of the saccharides is in the range of from 0.01 to 70% by weight.

15. The composition of Claim 6 wherein the amount of polyalcohols is in the range of from about 0.1 to 90% by weight.

16. The composition of Claim 1 further comprising at least one additive selected from viscosity modifiers or bonding enhancers or combination thereof.

17. The composition of Claim 16 wherein the amount of said additives is no more than about 65% by weight.

18. The composition of Claim 1 wherein energy is added to the composition in an amount sufficient to change the rate of which the drug is released from the composition or to bind the composition to a substrate.

19. The composition of Claim 1 wherein the composition is heated to a temperature of from about 40 to 200°C.

20. The composition of Claim 19 wherein the composition is heated at atmospheric pressure at sea level (about 760 mm Hg).

21. The composition of Claim 1 further comprising at least one dye compound.

22. The composition of Claim 21 wherein the dye compound is present in an amount of from about 0.01 to 50% by weight.

23. A drug delivery composition comprising:

a) at least one peptide selected from albumin or collagen in an amount of from about 1 to 35% by weight; and

b) hyaluronic acid, sodium salts thereof or chondroitin sulfate in an amount of 0.01 to 75% by weight; and

(c) at least one drug.

24. A method of administering a drug to a warm blooded animal comprising administering an effective amount of the composition of Claim 1 to said warm blooded animal.

25. The method of Claim 24 further comprising adding to the composition and amount of energy sufficient to change the rate at which the drug is released from the composition or to bind the composition to a substrate.

26. The method of Claim 25 wherein the composition is heated to a temperature of from about 40 to 200°C.

27. The method of Claim 24 wherein the composition further comprises at least one dye compound.

28. The method of Claim 25 wherein the energy has a wavelength in the electromagnetic spectrum selected from monochromatic coherent light, monochromatic non-coherent light, polychromatic coherent light, and polychromatic non-coherent light.

INTERNATIONAL SEARCH REPORT PCT/US92/00723

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): A61K 37/02, 37/12, 47/26
U.S. CL. 514/2, 54, 62

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System [5]	Classification Symbols
U.S.	514/2, 8, 21, 54, 62, 801, 604/20

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [6]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category * [15]	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	US, A, 4,291,013 (WAHLIG) 22 SEPTEMBER 1981 See the Abstract; column 2, line 36; column 3, line 6 through column 6, line 53; column 7, line 12 and Example 1.	1-6, 16-20 and 24-26
X	US, A, 4,849,141 (FUJIOKA) 18 JULY 1989 See the Abstract; column 2, line 8; column 3, line 8; column 5, line 34 and column 6, line 45.	1-8, 13 and 16-28
Y	Thorac. cardiovasc. surgeon, Volume 32, 1984, (DEYERLING) "A Suspension of Fibrin Glue and Antibiotic for Local Treatment of Myocotic Aneurysms in Endocardis - An Experimental Study", pages 369-372. See the Abstract.	21, 22 and 27

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
07 April 1992	11 MAY 1992
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	Thurman K. Page

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . because they relate to subject matter [2] not required to be searched by this Authority, namely:

2. ☐ Claim numbers . because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [3], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

The invention does not comply with PCT Rule 13 because of the presence of the following species.
1) proteoglycans 2) glycoproteins 3) protein gels-gelatin 4) saccharides 5) polyalcohols.

(continued)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

1-8, 13 and 16-28

4 ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Detailed Reasons for Holding the Invention as Lacking the Unity:

The species are patentably distinct and a search is needed in different areas of class 514 for each of the species specified. Note the following:

1. proteoglycans, subclass 62
2. glycoproteins subclass 2
3. saccharides subclass 53 through 61
4. polyalcohols subclass 738
5. protein gels, gelatin subclass 944

There is nothing of record to establish the species to be obvious variants.